Editorial

Immune checkpoint blockade (ICB) for first line treatment in non-small cell lung cancer (NSCLC)

Rafael Rosell[1,2], Niki Karachaliou[3], Aaron Sosa[3], Santiago Viteri[4]

[1]Germans Trias i Pujol Health Sciences Institute and Hospital, Badalona, Barcelona, Spain; [2]Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [3]Dr Rosell Oncology Institute (IOR), University Hospital Sagrat Cor, Barcelona, Spain; [4]Dr Rosell Oncology Institute (IOR), Quirón-Dexeus University Institute, Barcelona, Spain

Correspondence to: Rafael Rosell, MD, PhD. Director, Cancer Biology & Precision Medicine Program. Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Ctra Canyet, s/n, 08916 Badalona, Spain. Email: rrosell@iconcologia.net.

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Non-small cell lung cancer (NSCLC) is a dismal disease with a significant death toll, since, at the time of diagnosis, the disease is frequently disseminated (Stage IV), or locally advanced, and rapidly evolves to metastatic disease. In spite of adjuvant therapy, recurrence after surgery often occurs. Response to cisplatin-based chemotherapy is meager and radiographic response only reaches 30% (incomplete or partial response), with a short progression free survival (PFS) of 4–5 months and median survival of 10–12 months, with or without the addition of bevacizumab or EGFR monoclonal antibodies. Immune checkpoint blockade (ICB) or immune checkpoint antibody inhibitors have revolutionized the treatment of lung cancer, as well as other tumors. Recent data show that ICB and pembrolizumab (a PD-1 inhibitor) induce response rate in brain metastases of melanoma and NSCLC patients in a similar proportion found in systemic disease, between 20–30% (1,2). Recently, in conjunction with Bristol Myers Squibb, a cooperative group of investigators from the US and Canada reported the use of nivolumab (PD-1 antibody) for the first time in first line advanced NSCLC (CheckMate 012 trial) (3). Fifty two patients received nivolumab at the standard dose of 3 mg/kg intravenously every 2 weeks. This was the first time that four ongoing complete responses were observed and the response was not associated with the degree of PD-L1 expression, although, numerically, the response rate was higher in patients with positive PD-L1 expression, 28%, than in those with no PD-L1 expression, 14%. Even though the median PFS was 3.6 months, the median overall survival of 19.4 months constitutes a new landmark in survival of patients with advanced NSCLC (3). The median survival was 16.8 months for patients with squamous NSCLC and was not reached for patients with non-squamous NSCLC. The 18 month overall survival rate was 57%. Tumor PD-L1 expression was not quantifiable in 12% of the patients. There was no clear association between PFS or overall survival and baseline PD-L1 expression. Tumor biopsies taken from patients before treatment with ICB may indicate a lack of PD-L1 expression, however, immune checkpoint antibody blockade enhances T-cell response and infiltration into tumor tissue. Therefore, ICB allows reinvigoration of T cells that release interferon-γ, inducing PD-L1 expression in tumor cells. Henceforth, a biopsy after ICB would show PD-L1 positive tumor cells. This observation leads to the conclusion that the expression of PD-L1 in tumor tissue should not be used as a predictive biomarker for selection or exclusion of patients for treatment with ICB (4,5). Two phase III trials have evaluated the efficacy of nivolumab in first line therapy (CheckMate 026 and CheckMate 227). CheckMate 227 assesses nivolumab alone or in combination with ipilumumab or cisplatin based chemotherapy with or without nivolumab [reviewed in (3)]. Whether or not PD-L1 expression and response rate are related to the type of immune checkpoint inhibitor is at present unknown. However, pembrolizumab, also an anti-PD-1 antibody, has been approved for use only in PD-L1 positive previously treated NSCLC patients. The great advantage of nivolumab is that it does not require tumor

PD-L1 expression for prescription. Are the response rates of nivolumab and pembrolizumab really different according to PD-L1 expression? Not really, if we compare the results of CheckMate 012 to those of pembrolizumab in the KEYNOTE-001 trial (6). In the latter, PD-L1 positivity was defined as a membranous staining in at least 1% of cells (neoplastic and intercalated mono-nuclear cells) between tumor nests or a distinctive staining pattern caused by infiltration of mono-nuclear inflammatory cells in the stroma, forming a banding pattern adjacent to tumor nests (6). Membranous PD-L1 expression in at least 50% of tumor cells (proportion score, >50) was selected as the cutoff (6). The pembrolizumab response rate was 55.2%, with a proportion score of 50%, including 43.9% in previously treated patients and 50% in previously untreated patients (6). The fact that nivolumab response was 50% in patients with 50% PD-L1 expression in the CheckMate 012 trial is of interest (3). Median PFS among patients with a proportion score of 50% was 12.5 months for previously untreated patients in the KEYNOTE 001 study (6) and 8.3 months in the CheckMate 012 study (3). It is true that, numerically, response rate declines according to the level of PD-L1 expression, (See sup Table S7 and S8 in the KEYNOTE study, as well as Table 4 in CheckMate 012), however response is also observed in PD-L1 negative tumors. In addition, the prevalence of patients with a proportion score of 50% is around 23% (6). In both studies, CheckMate 012 and KEYNOTE 001, responses were higher in patients with KRAS mutations and KRAS mutations had increased PD-L1 staining (6). Patients with EGFR mutations responded less to nivolumab and pembrolizumab (3,6). It has been clearly announced that other predictive biomarkers should be kept in mind, including the presence of pre-existing CD8+ T cells and cytokines in tumor samples which could supplement PD-L1 expression in order to better identify patients that could respond to ICB (4-6).

It is rather interesting that interferon-γ related genes, including signal transducer and activation of transcription 1 (STAT1), have been associated with better clinical outcome in pembrolizumab treated metastatic squamous cell carcinoma of head and neck (KEYNOTE 012) (7). Along the same lines, in melanoma, resistance to PD-1 blockade has been seen to be related to a lack of response to interferon-γ. Western blot analysis shows that one baseline cell line responded to interferon-γ with the expected signal transduction, including an increase in STAT1, an interferon regulatory factor (IRF), expression, STAT1 phosphorylation and the production of downstream interferon targets, such as PD-L1 and major histocompatibility complex (MHC) class I. However, the cell line from the progression lesion shows a lack of response to interferon-γ (8). Of interest is the fact that in NSCLC the activation of STAT3 leads to activation of DNMTs, which further methylate the promoter region of STAT1 and key molecules such as IRF1 and proteasome subunits, PSMB8, PSMB9 and HLA molecules (9). It is well known that chemotherapy and radiotherapy can enhance response to ICB by the release of damage associated molecular patterns (DAMPS) [Reviewed in (5)]. Calreticulin is considered an essential DAMP and recent evidence shows that calreticulin expression in NSCLCs is associated with intra-tumoral infiltration of CD8+ T lymphocytes and predicts favorable response to ICB (10).

Of interest is the fact that other investigators in the POPLAR study, comparing atezolizumab (PD-L1 antibody) with docetaxel in previously treated NSCLC patients, showed that patients with pre-existing immunity, defined by high T-effector-interferon-γ-associated gene expression, had improved overall survival with atezolizumab. Survival benefit from atezolizumab increased with increasing PD-L1 expression on tumor cells, tumor infiltrating immune cells, or both. Median overall survival was 15.5 months for patients with a proportion score of 50% or more of PD-L1 expressing tumor cells or tumor infiltrating immune cells (11). Other anti-PD-L1 antibodies, such as avelumab, are very promising, since, in addition to anti-PD-L1 activity, avelumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC), contributing to the lysis of tumor cells (12). Purified natural killer (NK) cells are potent effectors for avelumab (12). Intriguingly, NK cells are tightly regulated by the JAK-STAT signaling pathways and cannot survive in the absence of STAT5 (13). At the same time, STAT5 repressed the transcription of VEGFA in NK cells, providing new clues for developing specific biomarkers for the assessment of avelumab therapy.

In summary, CheckMate 012 paved the way for the use of ICB as a novel therapy in NSCLC patients, mainly in smokers and those harboring KRAS mutations, with the first hints of complete responses in metastatic NSCLC and the observation that responses are durable and median survival exceeds, by far, those obtained by chemotherapy. The concept of DAMPS released by chemotherapy encourages the promotion of studies with the combination of chemotherapy and ICB. Several layers of evidence further pave the way for a more accurate predictive biomarker

scenario. Some new PD-L1 antibodies, such as avelumab with ADCC activity, could provide further advantages.

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Footnote

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